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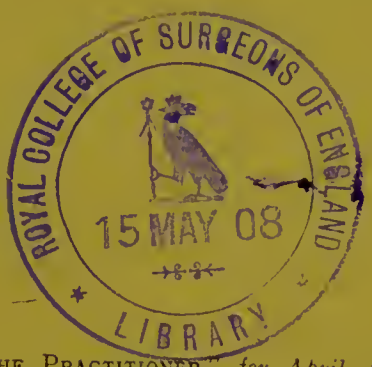

From "THE PRACTITIONER" *for April*, 1908.

POLYCYTHÆMIA IN DISEASES OF THE HEART AND LUNGS AND DURING RESIDENCE AT HIGH ALTITUDES.

BY F. PARKES WEBER, M.D., F.R.C.P.,

Physician to the German Hospital, London, and to the Mount Vernon Hospital for Chest Diseases, Hampstead.

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POLYCYTHÆMIA IN DISEASES OF THE HEART AND LUNGS AND DURING RESIDENCE AT HIGH ALTITUDES.[1]

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IN healthy men the average number of red corpuscles in a cubic millimetre of blood is roughly taken as about five millions, in women, it is slightly less. "Polycythæmia," or more exactly, "polycythæmia rubra," that is to say, an abnormally large number of red cells in the cubic millimetre of the blood, may be of two kinds, absolute and merely relative.

(1) Mere relative polycythæmia is due to concentration of the blood, such as may be caused by choleraic diarrhœa or other excessive fluid discharges from the body (copious sweating). It is doubtless almost always of only temporary occurrence (possible exceptions occur in some cases of recurring night-sweats, etc.), and the diminution in volume of the blood-plasma, which causes it, is quickly recovered from when the normal osmotic conditions are re-established. Some degree of local relative polycythæmia can be induced (experimentally or by disease) in one limb or in one part of the body by obstruction to the return of venous blood from the part in question; the explanation of this is that the delay of the blood-flow allows longer time for lymph to leave the blood-vessels, and so gives rise to local blood-concentration.

(2) In absolute or true polycythæmia (polycythæmia rubra vera) the total number of red corpuscles in the body is increased, and there is evidence to show that in most if not in all cases of absolute polycythæmia the total volume of blood in the body is increased as well as the number of corpuscles. It is quite probable that in certain patients with cardiac valvular defects, etc., a condition of absolute polycythæmia exists unaccompanied (owing to simultaneous relatively greater increase in the total volume of blood) by relative polycythæmia, but we need now only consider those

[1] The substance of a lecture delivered at the Mount Vernon Hospital Post-graduate Course.

cases in which the presence of absolute polycythæmia is evidenced by the persistence of a relative polycythæmia discovered on making a blood-count in the ordinary way.

The possibility of cases of absolute polycythæmia being regarded as cases of mere relative polycythæmia (*i.e.*, mere blood-concentration) is unlikely for the following reasons:—

(1) The absence of the recognised causes (diarrhœa, excessive sweating, etc.) of diminution in the total quantity of blood.

(2) The plethoric (full-blooded) or congested appearance of the patient.

(3) The persistence of the polycythæmia (merely relative polycythæmia, as already stated, is almost always only temporary).

(4) In some cases, moreover, as we shall subsequently point out, the total quantity of blood in the body can be estimated and proved to be in excess of the average.

Cases of absolute polycythæmia may be divided into the following classes:—

A.—Those due to imperfect oxygenation of the blood and tissues owing to circulatory disturbance in chronic cardiac and pulmonary diseases. To this class we might add the polycythæmia occasionally following carbon monoxide poisoning and other toxic conditions interfering with the proper oxygenation of the blood.

B.—Those connected with living at high altitudes and diminished oxygen-tension in the inspired air.

C.—Those classed under the heading "Splenomegalic Polycythæmia," or, as I have termed them, "Myelopathic Polycythæmia."

In all these classes of absolute polycythæmia, but especially in Class C., the increase in the number of red cells is sometimes very remarkable. In cases of congenital heart disease, with more or less chronic cyanosis, blood-counts of seven to eight million red cells to the cubic millimetre are not at all unusual, as in the case of a girl, aged 17 years, whom I showed at the Clinical Society of London in 1907,[1] and whose red corpuscles had varied from 6,375,000 to 7,352,000 in the cubic millimetre.

[1] *Clinical Society's Transactions*, Vol. XL., p. 251.

In a woman aged 21 years with congenital heart disease and cyanosis, H. Batty Shaw [1] recorded a count of 8,320,000 red cells, and a hæmoglobin-value of 150 per cent. of the normal standard. Some authors formerly thought that in chronic cyanosis connected with heart disease the red corpuscles never exceeded eight millions per cubic millimetre, but Friedel Pick as far back as 1904 reported a case of congenital pulmonary stenosis in a seven-year-old girl with a blood-count of over ten million red cells.[2] Quite recently at the Clinical Section of the Royal Society of Medicine (November 8th, 1907), Murray Leslie showed a woman aged 22 years with congenital heart disease, who had cyanosis and clubbing of the fingers from birth, and whose blood was found to contain over 11,000,000 red cells to the cubic millimetre. In three patients at the German Hospital with cyanosis connected with chronic pulmonary emphysema and circulatory insufficiency we obtained blood-counts of respectively 6,350,000, 6,850,000 and 6,870,000 red cells per cubic millimetre, and in a fourth case the counts on various occasions were 6,930,000, 8,230,000 and 9,357,000. In normal persons the "polycythæmia of high altitudes" (including that of residence at localities 6,000 feet or more above sea level) may reach seven to eight million red cells per cubic millimetre of blood. In cases of so-called splenomegalic polycythæmia, however, counts of nine to ten million red cells and over have been fairly common, with hæmoglobin-values up to 160 to 180 per cent. of the normal standard, and even higher. If samples of such extremely polycythæmic blood (in which coagulation has been prevented by the addition of citrate or tartrate of potassium) are allowed to stand in a cylindrical glass vessel until the corpuscles have had time to settle down, it will be found that the corpuscular sediment occupies over nine-tenths of the whole column, the blood-plasma forming only a thin layer on the surface; whereas in normal human blood the corpuscular layer and the layer of blood-plasma are about equal in volume.[3]

[1] *Clinical Society's Transactions*, Vol. XL., 259.

[2] Verein Deutscher Aertze in Prag, 22nd January, 1004.

[3] There is said not to be even "standing-room" for more than about thirteen million red blood-cells to the cubic millimetre, as Dr. R. Hutchison has expressed it. Yet blood counts of more than thirteen million red cells to the cubic millimetre have been recorded by some observers.

It is probable, as I have already mentioned, that in absolute polycythæmia the total volume of blood in the body is generally, if not always, above rather than below the normal average, that is to say, the quantity which should correspond to the body weight. In 1900 J. S. Haldane and Lorrain Smith published their "carbon monoxide method" of estimating the total volume of blood in the body,[1] a method which made it clinically possible to recognise the presence of true plethora, and in 1906 C. G. Douglas[2] tested this method in animals and found that the results obtained by it agreed fairly closely with those obtained by the old Welcker's method in which the blood had to be extracted from the tissues after the death of the animal. The carbon monoxide method has been already employed in various cases of true polycythæmia in man. Lorrain Smith and H. L. McKisack,[3] in the case of a boy, aged 12 years, suffering from adherent pericardium and chronic cyanosis, not only showed that the proportion of red cells to blood-plasma was excessive (relative polycythæmia), but also demonstrated by the carbon monoxide method that the total volume of blood was far beyond the normal standard, so that there was undoubtedly a condition of true plethora present. The number of red cells in the cubic millimetre of blood was 6,340,000, and by the carbon monoxide method it was ascertained that the total volume of blood in this boy's body was nearly double that of the normal standard. In the case of splenomegalic polycythæmia which I described in Volume LXXXVIII. of the *Medico-Chirurgical Transactions*[4] the total volume of the patient's blood was estimated in the same way by Haldane himself, and was found to be greatly in excess of the normal. In fact with a blood-count of between eight and nine million red cells to the cubic millimetre and with a hæmoglobin-value, of about 150 per cent. of the normal standard, there was likewise a great excess of the total blood-volume, that is to say, a condition of true plethora was also present. This is exactly what one would suppose from the plethoric look of such

[1] *Journal of Physiology*, London, 1900, Vol. XXV., p. 331.
[2] *Journal of Physiology*, 1906, Vol. XXXIII., p. 493.
[3] *Transactions of the Pathological Society of London*, 1902, Vol. LIII., p. 136.
[4] *Medico-Chirurgical Transactions*, London, 1905, Vol. LXXXVIII., p. 191.

patients and from the engorged state of their visceral blood-vessels as revealed at the few post-mortem examinations which have as yet been recorded. I have Dr. T. D. Acland's permission to state that in an as yet unpublished case of splenomegalic polycythæmia under his care at St. Thomas's Hospital, Dr. Haldane made a clinical estimation of the total blood-volume by the carbon monoxide method and showed that it was about two and half times the normal. Dr. R. Hutchison also kindly informs me that in two typical cases of splenomegalic polycythæmia (accounts of which have not yet been published) at the London Hospital Dr. A. E. Boycott determined the total blood-volume by Haldane and Lorrain Smith's method and found it in both cases very much increased, in one of the two cases indeed it appeared to reach the extraordinary figure of 10,750 cubic centimetres, that is to say, probably more than three times the volume normally corresponding to the patient's body-weight. In regard to the polycythæmia of high altitudes there is less evidence of associated polyæmia (true plethora) in human beings, but A. Jaquet and F. Suter[1] found that in rabbits kept at high altitudes (Davos) a very striking increase occurred, not only in the number of red corpuscles and richness in hæmoglobin per cubic millimetre of blood, but likewise in the total quantity of blood (and hæmoglobin) which could be extracted from the body.

What is the cause of the numerical increase of the red-blood corpuscles in the various classes of absolute (true) polycythæmia? In regard to the polycythæmia of chronic cardiac and pulmonary diseases there can now be no doubt that imperfect oxygenation of the blood and tissues is the exciting cause of the polycythæmia, in fact, that deficiency of oxygen, as was many years ago suggested, stimulates the functions of the red bone-marrow so as to cause an increased formation of red cells According to this view the polycythæmia is a "conservative" or "compensatory" vital reaction on the part of the individual, an automatic attempt to make up for deficient oxygenation of the tissues by increase in the number of the red blood-cells, which are the oxygen-carriers of the blood. Post-mortem examinations in cases of chronic cyanosis of cardiac or pulmo-

[1] *Korrespondenzblatt für Schweizer Aerzte*, 1898, No. 4.

nary origin help to confirm this hypothesis, for, in such cases, although the red colour of the bone-marrow of the shafts of the long bones is partly due, as I have satisfied myself, merely to engorgement with blood, evidence of abnormal hæmopoietic activity is likewise obtained. It is surprising, however, that in this respect very few exact observations have as yet been recorded. The polycythæmia of high altitudes,[1] which is now at last universally allowed to be an absolute or true polycythæmia, must be explained in the same way, as indeed F. Miescher suggested in 1893.[2] It represents, in fact, a conservative vital reaction on the part of the individual (that is to say, on the part of his bone-marrow) to compensate for the diminished oxygen-tension in the inspired air at high altitudes, *i.e.*, to compensate for the resulting difficulty in maintaining proper oxygenation of the blood and tissues of the body. Animals when kept at high altitudes react by a polycythæmia just as men do, and the bone-marrow of dogs which have developed a polycythæmia from being kept at high altitudes, has been carefully macroscopically and microscopically examined and found to give abundant evidence of increased erythropoietic activity.[3] I have already quoted Jaquet and Suter's observations on the increase of blood-corpuscles and hæmoglobin in rabbits when kept at Davos, the famous Swiss mountain resort. Jaquet[4] obtained quite similar results (nearly parallel increase in the figures) by keeping rabbits in chambers, in which the atmospheric pressure was artificially reduced[5] to correspond to a fall of 100 mm. in the height of the barometic column, which is equivalent to a rise of over 1,000 metres in altitude. Similar experiments

[1] Most of the very extensive literature on this subject was recently shortly summed up in *Climatotherapy and Balneotherapy*, by Sir H. Weber and F. Parkes Weber, Third Edition, London, 1907, pp. 60–62.

[2] *Korrespondenzblatt für Schweizer Aertze*, 1893, No. 24.

[3] See *Höhenklima und Bergwanderungen*, by N. Zuntz, A. Loewy, F. Müller and W. Caspari. Berlin, 1906, pp. 198–200.

[4] *Arch. fur exper. Pathologie u. Pharm.*, 1901, Vol. XLV., p. 1.

[5] Paul Regnard (*La Cure d'Altitude*, Paris, 1897) had already maintained that in animals an artificial atmosphere containing excess of oxygen reduced the number of red cells in the blood, and he had also increased the hæmoglobin-value of the blood by subjecting animals to an artificially rarefied atmosphere. But the value of his results was called in question owing to the artificial conditions to which the animals were subjected and by the possibility of excess of carbonic acid playing a part in the latter experiment.

had been carried out by O. Schaumann and E. Rosenquist [1] on dogs, rabbits, and pigeons. They were kept in an artificially extremely rarefied atmosphere, corresponding to an altitude of about 4,000 metres, and by this means not only were the red cells (erythrocytes) increased in number, but in the case of the dogs and rabbits nucleated red cells (erythroblasts), that is to say, young unripe forms of red cells, were made to enter the circulating blood from their normal home in the bone-marrow. Various observations quoted by Jaquet and others show that the changes in the quality and quantity of the blood which occur as the result of living at high altitudes and which can be experimentally produced by subjecting animals to an artificially rarefied atmosphere, cannot be explained as the effects of low temperature or increased light. As further confirmation of these views it may be mentioned that E. Kuhn [2] by the use of his so-called "suction-mask," that is to say, by periodical artificial diminution of the oxygen-pressure in the lungs has apparently been able to produce a decided increase of red cells in the blood.[3]

In regard to the cause of the polycythæmia in cases of so-called "splenomegalic polycythæmia" (a numerical increase in the red cells which, owing to the appearance of cyanosis, might, on first examination, in some cases be mistaken for that dependent on chronic cardiac or pulmonary direases), nothing certain is at present known, excepting that, as the changes found in the marrow of the shafts of the long bones at post-mortem examinations have shown, it is brought about by increased activity in the erythropoietic functions of the bone-marrow. But an increased activity of the bone-marrow is doubtless also the immediate cause of the other classes of absolute polycythæmia, as I have already pointed out when discussing the classes of polycythæmia dependent on chronic cardiac and pulmonary diseases, or on residence at high altitudes. There is no evidence that increased durability of the red corpuscles (increased resistance of the corpuscles

[1] "Ueber die Natur der Blutveranderungen im Höhenklima," *Zeitschrift für klin. Medizin*, Berlin, 1898, Vol. XXXV., p. 126 and p. 315.

[2] *Münchener med. Wochenschrift*, 1907, No. 35, p. 1713.

[3] I may here mention, however, that I am not at all convinced of the general clinical applicability of Kuhn's "suction-mask" (which I have myself, however, tried in only very few cases) for producing an increase of red cells and hæmoglobin in the blood of anæmic and tuberculous patients.

towards hæmolysis, etc.) plays any essential part in the causation of any kind of polycythæmia.

The relation of absolute polycythæmia (polycythæmia vera) to polyæmia (plethora vera).—Not many years ago the possibility of the persistence of a condition of plethora was denied by most authorities. R. von Limbeck, in the second edition (English translation, 1901) of his *Clinical Pathology of the Blood*,[1] wrote:—"The doctrine of plethora, formerly a dogma, has received its death-blow, owing to the growth of experimental investigation. It was especially due to the works of von Lesser, Worm-Müller, and Cohnheim that the possibility of the persistence of a condition of plethora came to be denied." In 1900, J. Lorrain Smith,[2] by the "carbon-monoxide method" previously referred to, proved that in the so-called anæmia of chlorosis, the volume of the blood was in reality greatly increased (in proportion to the severity of the disease), and now, as we have already pointed out, it appears that true (absolute and persistent) polycythæmia is always or almost always associated with a condition of true plethora (polyæmia).

Are there any experimental observations which throw light on this association of true plethora with polycythæmia? Yes, I think there are some, and, curiously enough, they are the very experiments of Worm-Müller (1875) on which Cohnheim based his assertion that plethora could not exist. These experiments and those of Von Lesser (1874) did, indeed, prove the impossibility of suddenly producing a persistent plethora by the experimental transfusion method, but, at the same time, they wonderfully well illustrate the manner in which a condition of persistent polycythæmic plethora may arise under certain pathological (chronic cardiac disease, etc.) or physiological (residence at high altitudes) conditions. I shall, therefore, shortly describe the experiments in question as given in Von Limbeck's work[3] already referred to. When Von Lesser and Worm-Müller tried to produce plethora artificially by transfusion of blood into an animal, the blood-vessels were at first enlarged to receive the excess and the blood-pressure was augmented, but a portion of the injected

[1] English translation by A. Latham and J. Nachbar, New Sydenham Society, 1901, p. 63.

[2] *Transactions of the Pathological Society of London*, 1900, Vol. LI., p. 311.

[3] *Loc. cit.*, p. 63.

blood quickly began to leave the vessels, the lymph-stream increased, and the increase in the blood-volume gave place to an increase of blood-corpuscles (polycythæmia), which in its turn gradually disappeared. No bad symptoms were observed when the quantity of blood transfused amounted even up to approximately 80 or 100 per cent. of the (estimated) normal total blood-volume in the animal's body. Within half an hour after the transfusion, half the injected fluid had already, according to Worm-Müller, left the blood-vessels, though the cellular elements remained, giving rise to a polycythæmia. In the case of a rabbit transfused for 15 minutes from another rabbit, the red corpuscles counted before the experiment were 5,160,000 to the cubic millimetre, but 22 minutes after the transfusion they were 8,280,000 to the cubic millimetre. In these experiments the polycythæmia did not last long. Worm-Müller found that the number of corpuscles was reduced to the normal in two days. Similarly, in the case of a dog in which the quantity of the blood was much increased by transfusion, the number of red corpuscles in the cubic millimetre of blood was found to be greatly in excess thirty minutes after the experiment, but here again the polycythæmia was only transitory, disappearing some days after the transfusion, though of course less quickly than the artificial plethora did.

In no such experiments have the conditions prevailing in the various classes of polycythæmic polyæmia (plethoric polycythæmia) (plethora vera) of human beings been fulfilled. In all these cases in human beings the polycythæmia, as we have explained, arises from increased activity in the hæmopoietic functions of the bone-marrow, and the increased activity of the bone-marrow is in its results practically equivalent to a gradual persistent transfusion of blood into the vessels. In other words the bone-marrow in these cases is constantly engaged in producing excess of blood, and forcing all of it into the blood-stream. The increased total quantity and polycythæmic quality of the circulating blood are both therefore the natural result of the persistent increased formation of blood in the bone-marrow, and a similar condition of persistent polycythæmia would be obtained in Worm-Müller's experiments on animals, were it possible (which of course is not) to modify his experiments, so as to make the transfusion of blood a gradual persistent process, lasting,

not for a few minutes, but for days, weeks, months, and years.

I think I have now sufficiently explained what I believe to be the only tenable views regarding the origin of the various classes of true (absolute) polycythæmia. They are all due to an increased hæmopoietic activity of the bone-marrow, that is to say, they are all myelogenous in origin, but although the exciting cause of this increased functional activity is recognised, as I have already explained, in regard to the polycythæmia connected with disorders of the circulatory system and life at high altitudes, it remains unknown in regard to the so-called "splenomegalic polycythæmia." In this last class of polycythæmia the excessive functional activity of the bone-marrow constitutes as yet the primary recognisable morbid factor, and that is the reason why, in 1905,[1] I proposed the term "myelopathic" (not merely myelogenous or myelogenic) polycythæmia for it. The excessive formation of red blood-corpuscles in myelopathic polycythæmia may perhaps be regarded as analogous to the excessive formation of white blood-corpuscles in cases of leukæmia. It has likewise been explained as the result of a morphological and functional reversion to a past condition (normal in fœtal life and early life after birth) in which the bone-marrow of the shafts of the long bones is red and still actively engaged in the formation of erythrocytes, instead of being yellow and fatty as most of it is in healthy adults. If the analogy to leukæmia proves to be appropriate, the term "erythræmia" employed by W. Türk,[2] Hans Hirschfield,[3] and by Osler[4] will be obviously preferable to the term "myelopathic polycythæmia" and the various other names which have been proposed, since it implies that the disease is one which in regard to erythrocyte-formation is analogous to leukæmia in regard to leucocyte-formation.[5]

[1] *Medico-Chirurgical Transactions*, London, 1905, Vol. LXXXVIII., p. 191.

[2] *Wiener klin. Wochenschrift*, 1904, No. 7, p. 192.

[3] *Berliner klin. Wochenschrift*, October 14th, 1907, p. 1302.

[4] *Lancet*, January 18th, 1908, p. 143.

[5] For possible objections to this view see J. Bence, *Deut. med. Wochenschrift*, 1906, No. 37, p. 1497, and F. Lommel, *Münchener med. Wochenschrift*, 1908, No. 6, p. 272. According to Bence, the polycythæmia of the so-called splenomegalic polycythæmia can be diminished by oxygenation-inhalation just as he claims that the polycythæmia of cardiac origin and that due to high altitudes can be. I suppose that in all such investigations the method of oxygen-inhalation employed would be such as effectually to increase the oxygen-tension in the inspired air.

The word "erythrocytosis" could then, as Hirschfield advises, be reserved for any "reactive" increase in the number of erythrocytes (such as the polycythæmia of cardiac insufficiency, and the polycythæmia of high altitudes) resulting from imperfect oxygenation of the blood and tissues of the body, just as the word "leucocytosis" is now limited to signify a "reactive" increase in the number of leucocytes, such as that resulting from (and as a reaction towards) streptococcal and other microbic invasions of the body.

The Relation of Polycythæmia to Blood-Viscosity.—The blood-viscosity is always raised when the number of red corpuscles per cubic millimetre of blood is much increased. This can be demonstrated, as I have myself found, in specimens of blood from patients with polycythæmia and chronic cyanosis of cardiac or pulmonary origin. So also in two cases of splenomegalic polycythæmia I found the viscosity of citrated specimens of the venesection-blood to be more than twice the normal. Supposing the viscosity of normal human blood to be about 5·3, that is to say, 5·3 times that of water (when the temperature of both is 38° C.), Lommel found the viscosity to be over 11·0 in one case of splenomegalic polycythæmia, whilst Bence in another case obtained figures varying from 15·9 to 20·9. In three cases of cyanosis in heart disease, and in one case of bronchitis with emphysema, Bence obtained viscosity-values of between 6·9 and 8·2. In some rough experiments made in 1904 with J. H. Watson on citrated horse's blood, we showed that the variations in viscosity generally depended mainly, though of course not entirely, on the proportion of the blood-corpuscles to the volume of blood-plasma. It was found, for instance, that horse's blood-plasma, artificially mixed with two millions of red corpuscles to the cubic millimetre, took 84 seconds to pass through the bulb of the "viscosity-tube," whilst a sample containing four million red corpuscles to the cubic millimetre took 110 seconds to pass through the bulb of the same tube.[1] There can be no doubt that blood-viscosity is of some importance in regard to the question of venesection in chronic diseases of the heart and lungs, since in cases of cyanosis with polycythæmia, increased blood-viscosity, and engorgement of the right side of the heart, venesection must not only temporarily relieve the right side of the heart, but

[1] *Clinical Society's Transactions*, London, 1904, Vol. 37, p. 130.

must also, by diluting the blood,[1] reduce its viscosity, and thus enable it to circulate more freely through the capillaries of the lungs and other organs. I believe that Determann's viscosimeter is one of the most convenient instruments at present to be obtained for clinically examining the viscosity of the blood. Only a very small sample of blood is required, no more than can be readily obtained by pricking the lobe of the ear. Coagulation is prevented by the use of "hirudin." The only drawback to Determann's method is that, according to his directions, the skin (that is, the lobe of the ear) may not be washed and thoroughly disinfected just before the puncture is made; but this objection should apply just as much to all "clinical viscosimeters" in which only a very small sample of blood is employed for estimating the viscosity.

There can be little doubt that in some individuals a condition of polycythæmia is produced (*i.e.*, as a vital reaction against deficient oxygenation of the blood and tissues) more easily than in others. Moreover, patients with chronic diseases of the heart and lungs, which ought to give rise to polycythæmia, may of course owing to special circumstances (that is to say, owing to factors other than imperfect oxygenation) be anæmic instead of polycythæmic. A practical result, however, of what I have explained in the present summary of the subject is that a person who is healthy except for some pulmonary or cardiac affection, which mechanically hinders normal oxygenation of the blood and tissues, should be expected to have blood differing in quality from that of a completely healthy person by its more or less greater richness in red corpuscles. This, I believe, is the chief reason why persons with incipient or old quiescent pulmonary tuberculosis, when well fed and otherwise properly treated in sanatoriums, often show a moderate degree of polycythæmia when a blood-count is taken.

[1] Some of the blood withdrawn by ordinary venesection from the blood-vessels is of course quickly replaced by water and salts absorbed from the alimentary canal, and thus venesection rapidly causes dilution of the circulating blood.

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